Damage Control for Renal Artery Stenting

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Chronic kidney disease is associated with an increased risk of death in ambulatory patients,1 patients with heart disease,2 and in those undergoing cardiac procedures.3 Slowing the progression of kidney damage should improve survival.

Stenting of atherosclerotic renal artery stenoses is commonly performed in an attempt to preserve renal function and control blood pressure. The number of Medicare recipients undergoing renal artery angioplasty or stent placement has increased strikingly from 7660 cases in 1996 to 18 520 cases in 2000,4 but evidence of benefit remains “sparse and inconclusive.”5

In this issue of Circulation, Cooper and colleagues report the results of a randomized trial of patients undergoing renal artery stenting to determine whether a filter-based embolic protection device (EPD), the platelet glycoprotein inhibitor abciximab, or both in combination improves renal function.6 The results were more negative than anticipated. Glomerular filtration rates (GFR) worsened 30 days after renal stenting in 3 treatment groups and remained unchanged in the fourth group treated with combination therapy (see Table). Secondary comparisons among the treatment groups suggested that the combination of an EPD with abciximab caused the smallest changes in GFR, but no treatment could improve renal function over that existing at baseline before renal artery stenting was carried out.

The investigators estimated GFR from the creatinine-based Modification of Diet in Renal Disease formula and corroborated the results with measurements of cystatin C. Cystatin C, a cysteine protease inhibitor produced by nearly all human cells, is a nonglycosylated basic protein with a low molecular mass (13 kDa) that is freely filtered by the glomerulus.7 When Cooper and colleagues used cystatin C to estimate GFR, they observed the same pattern of deterioration in renal function and no significant differences among the treatment groups.

Although the current study focused on therapies to prevent microembolism, the results have broader implications. The failure of this well-designed trial to achieve its prospectively defined end points challenges some commonly held assumptions about atherosclerotic renal artery disease and the reversibility of renal injury.

The study enrolled patients with renal artery stenoses greater than or equal to a 50%-diameter reduction,8 a generally accepted9 but not universally recommended angiographic threshold for stenting.9 The physiological principles defining the minimal critical stenosis needed to reduce perfusion vary from organ to organ. Renal blood flow is ≈400 mL/min per 100 g of tissue, which is 5 to 50 times more than the flow through other organs, and the arteriovenous oxygen difference is low at 1 to 2 mL/dL.10 In comparison, resting coronary blood flow ranges from 50 to 80 mL/min per 100 g of tissue, and the arteriovenous oxygen difference is high at 16 mL/dL.11 Resting coronary blood flow falls in the presence of an 80%-stenosis, but maximal coronary flow reserve begins to fall at about a 50%-diameter stenosis. This is defined as the minimal critical stenosis in the coronary circulation, because flow may need to increase as much as 5-fold when myocardial oxygen consumption rises during exercise.11 The concept of renal flow reserve differs from that for the coronary circulation because oxygen is delivered at rest in marked excess of that required to meet the metabolic needs of the renal parenchyma, and autoregulatory mechanisms increase renal blood flow in the presence of low perfusion pressure.10

In dogs with innervated or denervated kidneys, perfusion pressure falls when diameter stenoses reach 50%.12 Augo-regulation of blood flow prevents other functional consequences until stenosis severity exceeds 70%, at which point blood pressure begins to rise (see Figure). Renal blood flow does not fall until stenosis severity is >75%.

The threshold stenosis in humans required to reduce renal function remains unknown. In clinical studies, the severity of atherosclerotic stenoses does not correlate with impairments in renal function. Split-kidney measurements in 79 patients with chronic kidney disease, made with a51chromium ethylenediamine tetraacetic acid technique, showed that individual kidneys with any severity of stenosis have a GFR the same as or higher than kidneys without a stenosis (17.3 mL/min versus 13.6 mL/min).13 In another study, patients with unilateral or bilateral renal stenoses had similar estimates of GFR (32.1 mL/min versus 32.7 mL/min), and no relation could be identified between stenosis severity and GFR or between stenosis severity and kidney size.14

Although atherosclerotic renal arterial stenoses are commonly associated with evidence of renal impairment, the frequent association does not prove causation. The explanation for the association is clear however: The conditions that cause hypertensive nephrosclerosis and diabetic nephropathy are also common risk factors for the development of atherosclerotic renal artery stenoses.5 Correction of a renal stenosis does not predictably improve renal function, whereas deterioration of function after stenting has potentially dire consequences. Mortality rates at an average of 21 months were...
compared with controls. During carotid interventions, EPDs are commonly used on the basis of evidence from randomized trials that have reported a halving in the rate of embolic debris have ranged from 84% during carotid stenting to 91% during aortocoronary bypass graft interventions. 

Table. Summary Results of the Primary (1°) End Point of Absolute Change in Glomerular Filtration Rate (ΔGFR) and Percentage Change From Baseline to 30 Days After Renal Artery Stenting Plus Abciximab, Filter-Based Embolic Protection, or Both

<table>
<thead>
<tr>
<th>Filter (−)</th>
<th>Abciximab (−)</th>
<th>Abciximab (+)</th>
<th>Row Summary</th>
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</thead>
<tbody>
<tr>
<td>1° end point</td>
<td>Stent alone (n=26)</td>
<td>Stent plus abciximab (n=21)</td>
<td></td>
</tr>
<tr>
<td>Absolute ΔGFR, mL/min</td>
<td>−7±16</td>
<td>−7±13</td>
<td></td>
</tr>
<tr>
<td>Relative ΔGFR, %</td>
<td>−10±20</td>
<td>−10±20</td>
<td>−10±20%</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Filter (+)</td>
<td>Stent plus filter (n=21)</td>
<td>Stent plus combination (n=23)</td>
<td></td>
</tr>
<tr>
<td>1° end point</td>
<td>61±29 to 52±22</td>
<td>52±18 to 54±19 (n=23)</td>
<td></td>
</tr>
<tr>
<td>Absolute ΔGFR, mL/min</td>
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<td>+2±14</td>
<td></td>
</tr>
<tr>
<td>Relative ΔGFR, %</td>
<td>−12±21</td>
<td>+9±30</td>
<td>−1±28%</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Column summary, ΔGFR, %</td>
<td>−10±20</td>
<td>0±27</td>
<td></td>
</tr>
</tbody>
</table>

strikingly higher when renal function had worsened after renal stenting than when it had improved (45% versus 0%). 

In an effort to improve the outcomes of renal stenting, the current study objectively evaluated endovascular therapies commonly used in other vascular beds to prevent atherothrombotic embolization. The use of glycoprotein IIb/IIIa inhibitors has been identified as a key therapy for patients with acute coronary syndromes undergoing native-vessel coronary intervention, but these agents have not been effective in all interventional settings. Platelet glycoprotein IIb/IIIa inhibitors have failed to show a benefit during aortocoronary bypass interventions in subgroup analyses of randomized trials carried out before the widespread use of EPDs and in retrospective analyses of more recent trials performed with EPDs. Platelet glycoprotein IIb/IIIa inhibitors are not used routinely during carotid stenting. An explanation for the lack of efficacy in these settings is that glycoprotein IIb/IIIa inhibitors do not protect the distal vasculature from the volume or type of atheromatous particulate matter embolized during large-vessel intervention.

During aortocoronary bypass graft interventions, EPDs are commonly used on the basis of evidence from randomized trials that have reported a halving in the rate of embolic complications and myocardial infarctions with EPDs as compared with controls. During carotid interventions, EPDs are used almost universally on the basis of analyses of historical controls. Rates of capture of atherothrombotic debris have ranged from 84% during carotid stenting to 91% during aortocoronary bypass graft interventions. Capture of atheromatous debris ranged from 17% to 21% of cases after renal stenting in the current study, which may reflect a lower rate during renal stenting than during carotid or aortocoronary bypass graft stenting. A possible explanation for the interaction between the filter-based EPD and abciximab seen in the current study may be that two mechanisms called the “filter paradox.” Whereas filter-based EPDs are designed to capture embolized material, these devices may inadvertently become the nidus of platelet aggregation in the presence of activated platelets, fibrinogen, and flow disruption; abciximab may block the aggregation of platelets on the filter surface under these circumstances.

Although the current study has been a commendable initiative to improve the outcome of stenting for atherosclerotic renal artery disease, the unanticipated outcomes call for a reality check. Renal artery stenting rarely produces immediate clinical benefits. Procedural complication rates of 4% to 10% and mortality rates of 1% seem a high price to pay for a small chance of improving renal function or theoretically preventing the progression to renal artery occlusion several years later.

Concerns about the limitations of renal artery stenting have been highlighted by the Agency for Healthcare Research and Quality (AHRQ), which commissioned a review of evidence and found little support for the routine practice. The Medicare Evidence Development and Coverage Advisory Committee (MedCAD) convened a meeting on July 18, 2007, to consider the basis for a national coverage determination (NCD), which could override the current reimbursement policies of local payers. Although no changes have been enacted, the preliminary report of the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial has raised additional concerns about renal artery stenting and should motivate enrollment in ongoing clinical trials such as the Cardiovascular Outcomes in Renovascular Lesions trial (CORAL, http://www.clinicaltrials.gov NCT00081731).

Current indications for renal stenting in the meantime should be limited to clinical conditions associated with renal artery stenoses jeopardizing a significant proportion of the nephron mass. Clinical conditions likely to benefit are those with severe bilateral disease with >70% stenoses associated with severe and refractory hypertension or flash pulmonary edema or possibly for deteriorating renal function despite optimal medical therapy.

The current report suggests that renal function may deteriorate despite the use of innovative methods to protect the renal vascular bed during renal artery stenting. Embolization may still occur at several procedural steps that cannot be protected by EPDs or with abciximab, such as catheter manipulation within shaggy atherosclerotic aortas, instrumentation of diseased renal ostia, or advancement of EPDs within renal arteries. Many operators use a “no-touch” technique to
navigate catheters through hostile aortorenal vascular beds, but a “hands-off” approach using optimal medical therapy may be the preferred strategy over renal stenting for most patients to prevent renal injury.

Disclosures

None.

References


Key Words: Editorials arteriosclerosis kidney stenosis stents

Figure. Relation between stenosis severity and mean blood pressure (A), renal perfusion pressure (B), and renal blood flow (C). Although renal perfusion falls when diameter stenosis is >50%, blood pressure does not rise until stenosis severity is >70%, and renal blood does not fall until stenosis severity is >75%. Reprinted from Imanishi et al with permission from the publisher. Copyright © 1992 Sage Publications Inc.